Placebo-Controlled Studies of Sustaining the Alertness and Flight Performance of Aviators with Dexedrine®

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SUMMARY

Dextroamphetamine (Dexedrine®) is a stimulant capable of temporarily reversing many of the effects of sleep deprivation. This report substantiates the efficacy of Dexedrine for aviation sustained operations. Specifically, it is shown that this countermeasure maintains flight skills, psychological mood, and physiological activation in sleep-deprived pilots. Dexedrine's positive impact is not offset by marked disruptions in recovery sleep, although "lighter sleep" was noted after the drug than after placebo. It is concluded that Dexedrine is a viable remedy for fatigue in aviation sustained operations, but it is not a substitute for proper crew-rest scheduling. There is no replacement for adequate restful sleep.

INTRODUCTION

In part, because of advances in night vision technologies and improvements in the reliability of new aircraft, it has become highly feasible for aviation units to operate around the clock for days and weeks at a time. In fact, such sustained operations now are viewed as a tactical necessity on the modern battlefield. Unfortunately, this creates difficulties from a personnel standpoint because it is difficult to ensure that soldiers are "at their best" during each duty cycle. Lengthy work periods can produce significant levels of fatigue due to circadian disruptions and insufficient sleep.

Humans need periodic sleep for the restoration of both the body and the brain (Horne, 1978), and ignoring this fact leads to cognitive impairments, attentional lapses, and slower reaction times (Krueger, 1989). Sleep-deprived personnel can be expected to lose approximately 25 percent of their ability to perform useful mental work with each 24-hour period of sleep loss (Belenky et al., 1994).

To ensure that soldiers, and aviators in particular, can continue to perform despite significant sleep debt, it is essential that effective fatigue countermeasures be developed and refined. Unfortunately, several fatigue remedies have been proposed, but few have been more than marginally successful.

Policy/administrative countermeasures

Limiting the amount of time that personnel may work (or fly) during any given 24-hour period is one important way to reduce fatigue. Research suggests that long work hours tend to adversely affect workplace safety while reducing health. In fact, a three-fold increase in industrial accidents has been found to occur after 16-hour work shifts (Rosa, 1995). Night work is particularly problematic when combined with overtime hours. Along these lines, it should be noted that several well-known catastrophes such as Three Mile Island, Chernobyl, Exxon Valdez, and the space shuttle Challenger all began in the early morning with errors made by personnel who had been on duty for extended periods. Thus, it is worthwhile to place restrictions on duty cycles. Unfortunately, the implementation of such restrictions has been less than optimal, partially because mission demands continue to grow while personnel and budgetary resources dwindle. This has certainly been the case in the U.S. Army (Department of the Army, 1996). Often, there simply is no choice except to "get the mission accomplished" no matter how tired the crews may be. In addition, it is clear that crew endurance guidelines suffer from the same types of problems as hours-of-service regulations have in the civilian transportation industry—they do not adequately incorporate scientific knowledge on sleep and circadian physiology (Dinges, Graeber, Rosekind, Samel & Wegmann, 1996). A variety of factors other than "time on task" (such as circadian phase, prior sleep quality, time since last sleep period, etc.) are directly related to crew performance, and these must be addressed to optimize mission readiness.

Behavioral countermeasures

There are a variety of behavioral countermeasures that might be undertaken by individuals in an attempt to improve their alertness in fatiguing situations. These consist of ensuring a high

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degree of physical fitness, engaging in physical exercise to attenuate drowsiness, or relying on naps to compensate for lost sleep. Unfortunately, napping is really the only one of these three strategies that actually works.

Physically-fit people are better able to withstand prolonged periods of physical work than those who are sedentary, but there is no evidence that fitness is able to stave off mental fatigue. In fact, Angus, Pigeau and Heslegrave (1992) found that highly fit individuals were no better at sustaining intense cognitive work than those who were less fit in situations where alertness was compromised by sleep-deprivation.

The usefulness of physical exercise is likewise doubtful. Brief periods of exercise have been shown to temporarily increase arousal in sleepy personnel (LeDuc, Caldwell, Ruyak, Prazinko, Gardner, Colon, Norman, Cruz, Jones, & Brock, 1998; Horne & Reyner, 1995; Angus et al., 1992), but the effects are too transient to be of much benefit to air crews working prolonged hours. Also, there is some evidence that intense exercise might actually produce an *increase* in sleepiness several minutes after the exercise session despite its initial tendency to boost performance.

Napping is the best "behavioral" fatigue countermeasure because sleep is the only antidote for sleep deprivation. Thus, in situations where some sleep (but not a full 8 hours) is possible, napping should be employed (Dinges & Broughton, 1989). Napping has proven extremely beneficial in aviation (Rosekind, Gander, Miller, Gregory, Smith, Weldon, Co, McNally & Lebacqz, 1994) and elsewhere (Stampi, 1992). Unfortunately, the implementation of this strategy in operational settings is often difficult because: 1) the environment is not conducive to sleep; 2) the schedules of personnel do not permit naps at appropriate times in the circadian cycle; and/or 3) unpredictable mission demands make it impossible to schedule proper napping periods.

Pharmacological countermeasures

When all else fails, stimulants are the best (and often the only) way to counter the effects of severe fatigue. Stimulants are effective and easy to use, and their feasibility is not dependent upon environmental manipulations or scheduling modifications. This explains why pharmacological compounds such as amphetamines have been used extensively in several military conflicts. Of course, there are other types of stimulants that are available as well (Akerstedt & Ficca, 1997); but to date, the amphetamines appear to offer the greatest potential for combating fatigue in sleep-deprived personnel.

The efficacy of dextroamphetamine (Dexedrine®) in particular has been well-established. In the field, Senechal (1988) reported the effective use of Dexedrine with EF-111A Raven jet crews during an Air Force strike on Libya in April of 1986, and Cornum (1992) indicated similar success sustaining the performance of F-15C pilots during combat air patrol missions in Operation Desert Shield/Storm. Emonson and Vanderbeek (1993) also reported that Air Force pilots effectively used dextroamphetamine during Operation Desert Storm. With Dexedrine, the aviators were better able to maintain acceptable performance during continuous and sustained missions without unwanted side effects.

In the Laboratory, the efficacy of Dexedrine has been established in several studies with sleep-deprived helicopter pilots. These studies, conducted at the U.S. Army Aeromedical Research Laboratory, have included three evaluations of Dexedrine® throughout 40 hours of continuous wakefulness and one throughout 64 hours sleep loss. Two of the 40-hour studies were conducted in a UH-60 helicopter flight simulator (Caldwell, Caldwell, Crowley & Jones, 1995; Caldwell, Caldwell & Crowley, 1997), and one 40-hour study was completed in an actual UH-60 aircraft (Caldwell & Caldwell, 1997a). The 64-hour study was performed in the simulator (Caldwell, Smythe, LeDuc & Caldwell 2000). Dexedrine was shown to be efficacious in terms of sustaining flight performance on a variety of precision "instrument" maneuvers despite severe levels of sleep deprivation. In fact, performance was maintained at or near baseline levels even after 50 hours of continuous wakefulness.

OBJECTIVE

The present report will present a unified summary of key findings from these previous investigations by combining multiple smaller data sets into larger-scale analyses. These analyses will focus on overall flight performance, electroencephalographic activity (EEG), subjective mood reports, and recovery-sleep data.

METHOD

Participants

Twenty-eight Army UH-60 helicopter pilots were tested. Their mean age was 29.6 years, and the mean amount of flight experience was 1,038 hours. Seven volunteers were female and 21 were male. All passed a medical prescreen to rule out significant illnesses of any type, sleep difficulties, allergic reactions to medications, etc., and all signed consent forms which fully disclosed any hazards associated with the experiments. Participants refrained from ingesting caffeinated products during the protocols.

Apparatus

UH-60 simulator. Simulator flights (performed in three of the four studies) were conducted in a specially-instrumented UH-60 simulator (CAE-Link Corporation, Model Trainer ASSY-2B38, Binghampton, NY) with computer-generated visuals, 6-degree-of-freedom motion base, and a multi-channel data acquisition system.

UH-60 aircraft. Aircraft flights (performed in one of the four studies) were conducted in a UH-60 helicopter (Sikorsky Aircraft, Stratford, CT) equipped with a computerized flight monitoring system. This system recorded the same aspects of pilot performance that were collected in the simulator studies.

Waking EEG. EEGs were recorded via Grass (Quincy, MA) E5SH electrodes (filled with SigmaGel electrolyte) from electrode site C_Z. Data were amplified and stored on a Cadwell Spectrum 32 (Kennewick, WA). The low and high filters were set at 0.53 and 20 Hz, respectively, and the 60 Hz notch filter was used.

Profile of Mood States (POMS). Mood was assessed with the POMS, a 65-item test which measures affect on six scales: 1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment (McNair, Lorr & Droppleman, 1981)

Polysomnographic evaluations. Sleep architecture during recovery sleep was examined using a Nihon Kohden electroencephalograph (model No. EEG-4321P, Irvine, CA). Data were recorded via Grass E5SH electrodes from C_3, C_4, O_1, and O_2 (referenced to contralateral mastoids). Electromyographic (EMG) and electrooculographic (EOG) data were recorded via SensorMedics electrodes placed under the chin (for EMG) and at the outer canthus of left and right eyes (for EOG). Time constants and high filter settings were: 0.3 sec. and 35 Hz for EEG, 5.0 sec. and 10 Hz for EOG, and 0.003 and 120 Hz for EMG.

Procedure

Volunteers arrived at the Laboratory on Sunday for prescreening and preparation. Training sessions were conducted at 0900, 1300, and 1700 on Monday (training day). On Tuesday (control) and Thursday (control), there were testing sessions at these times as well. On Wednesday (the deprivation day in the first cycle), and on Friday (the deprivation day in the second cycle), testing sessions occurred at 0100, 0500, 0900, 1300, and 1700. On these days, drug or placebo doses were administered at 0000, 0400, and 0800. At each dose time, subjects received 10 mg Dexedrine or matching placebo. The study was double blind and counterbalanced, and subjects were randomly assigned to a specific drug/placebo order upon arrival.

The two deprivation cycles (Tuesday/Wednesday and Thursday/Friday) were separated by an 8-hour recovery sleep. The deprivation cycles began at 0700 on the morning of one day and ended at 2300 on the night of the following day. Each deprivation cycle included eight testing sessions at the times noted above. Each session began with a 1-hour flight, continued with the EEG (approximately 20 minutes after the flight), and concluded with the POMS (approximately 1 hour and 20 minutes after each flight).

Flights. There were 14 maneuvers of the type typically flown in a UH-60 helicopter. Included were straight-and-level (SL) segments, left and right standard-rate turns (LSRTs and RSRTs), climbs, descents, and a left-descending turn (LDT). During each maneuver, subjects were required to maintain an airspeed of 120 knots, but specific targets for heading and altitudes changed from maneuver to maneuver. Subjects were instructed to make all turns at a standard rate of 3 degrees per second (or 20 degrees of roll angle) and to perform climbs and descents at a standard rate of 500 feet per minute.

Based on the data collected on each individual maneuver, scores ranging from 0-100 (with 100 reflecting near perfect accuracy) were calculated for a variety of measures. These scores, based upon the extent to which subjects deviated from ideal target values, expressed how well subjects maintained headings, altitudes, airspeeds, and other parameters. The scoring bands for each parameter are listed in the table. Individual parameter scores were averaged to produce one composite flight score for each iteration of each maneuver.

Table. Scoring parameters for flight data.

	Maximum deviation for scores of:					
Measure (units)	100.0	80.0	60.0	40.0	20.0	0.0
Heading (deg)	1.0	2.0	4.0	8.0	16.0	>16.0
Altitude (ft)	8.8	17.5	35.0	70.0	140.0	>140.0
Airspeed (knts)	1.3	2.5	5.0	10.0	20.0	>20.0
Slip (ball width)	0.0	0.1	0.2	0.4	0.8	>0.8
Roll (deg)	0.8	1.5	3.0	6.0	12.0	>12.0
Vert. Speed (ft/m)	10.0	20.0	40.0	80.0	160.0	>160.0
Turn Rate (deg/s)	3.0	5.0	10.0	20.0	40.0	>40.0

Waking EEGs. EEG sessions occurred approximately 20 minutes after the flights. In each session, data were collected under eyes open and eyes closed conditions, for 1.5-minutes per condition. Data were recorded from F_z, C_z, and P_z, referenced to linked mastoids (impedances were 5,000 ohms or less), but only the C_z data will be reported here because the results from the other electrodes were found to be redundant. For scoring the data, each EEG record was visually scanned for three relatively artifact-free 2.5-second epochs (per eyes-open and eyes-closed iteration). Based on these EEG epochs, absolute

power values expressed in millivolts squared were calculated for each of four frequency bands: delta (1.0-3.5Hz), theta (3.5-8.0 Hz), alpha (8.0-13.0 Hz) and beta (13.0-20.0 Hz). However, since theta activity is the most uniformly accepted EEG indication of significant fatigue from sleep deprivation, it will be the only EEG data included in the combined analysis.

POMS. The POMS was given approximately 1 hour after the EEG. Subjects indicated on a standardized form how well each of 65 mood adjectives described the way he/she was presently feeling. Six factors (mentioned previously) were derived via computerized or hand scoring.

Polysomnography. On each of the nights when sleep was allowed, subjects slept for approximately 8 hours while electrophysiological data (EEG, EOG and EMG) were recorded. Recordings were made at the beginning of the study (baseline) and following each deprivation cycle. Thus, there were 3 nights in which sleep architecture data were obtained for analysis (i.e., the baseline night, the Dexedrine recovery night, and the placebo recovery night). The sleep data from each of these nights were scored according to the rules set forth by Rechtschaffen & Kales (1968). Although several parameters were calculated, the percentages of time subjects spent in stages 1-4 and rapid eye movement (REM) sleep will be the only data reported here.

RESULTS

Flight Performance

Flight performance scores from the four studies were analyzed for differences under placebo versus Dexedrine across the baseline flights (at 0900, 1300, and 1700) and deprivation flights (0100, 0500, 0900, 1300 and 1700) averaged across the six types of maneuvers (SL, LSRT, RSRT, Climb, Descent, and LDT). Only drug-related main effects and interactions are presented here for the sake of brevity.

A 3-way interaction among study, drug, and session ($F(18.06,144.46)=2.07$, $p=.0097$) was due to larger drug-by-session differences in the simulator protocols than in the in-flight protocol. Follow-up analyses indicated that performance was better under Dexedrine than placebo at three sessions (0500, 0900, and 1700) in the 40-hour simulator protocol with males; at three sessions (0500, 0900, and 1300) in the 40-hour simulator protocol with females; and at four sessions (0500, 0900, 1300, and 1700) in the first 40 hours of the 64-hour simulator protocol. However, differences in the in-flight study were found only at 0900. There was a consistent 2-way interaction between drug and session ($F(6.02,144.46)=16.87$, $p<.0001$) as well (see figure 1). This resulted from the lack of any baseline differences followed by significantly better performance under Dexedrine than placebo at each of the deprivation sessions from 0500 to 1700 across all of the maneuvers flown ($p<.05$). There was a drug main effect ($F(1,24)=21.30$, $p=.0001$) which was attributable to better overall performance under Dexedrine than placebo.

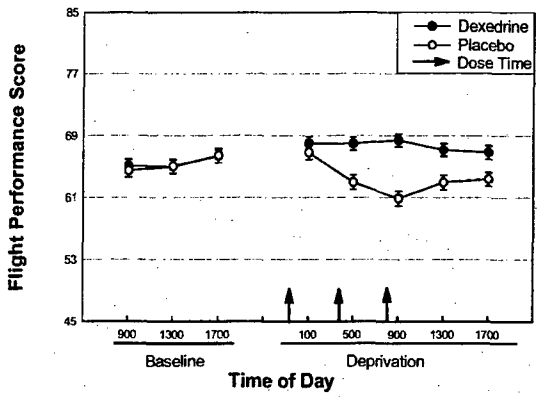

Figure 1. Performance was sustained at baseline levels by Dexedrine, but suffered under placebo.

EEG theta activity

Absolute power in the theta band from the eyes-open/eyes-closed EEG were analyzed with analyses of variance (ANOVAs) consisting of four factors: study (three simulator and one in-flight investigation), drug (placebo versus Dexedrine), session (1020, 1420, and 1820 on baseline; and 0220, 0620, 1020, 1420, and 1820 on the deprivation day), and eyes (eyes open/eyes closed).

There were two drug-related interactions. The first was a drug-by-eyes interaction ($F(1,23)=13.15$, $p=.0014$) that occurred because there were larger differences between Dexedrine and placebo under eyes-closed than eyes-open. The second was a drug-by-session interaction ($F(7,161)=5.83$, $p<.0001$) which was partially due to a peculiar reversal of EEG effects from the first baseline session compared to the last four deprivation sessions (see figure 2). There was more theta in the first Dexedrine baseline session than on the first placebo baseline session, but the opposite occurred at the sleep-deprivation times from 0620 to 1820 ($p<.05$).

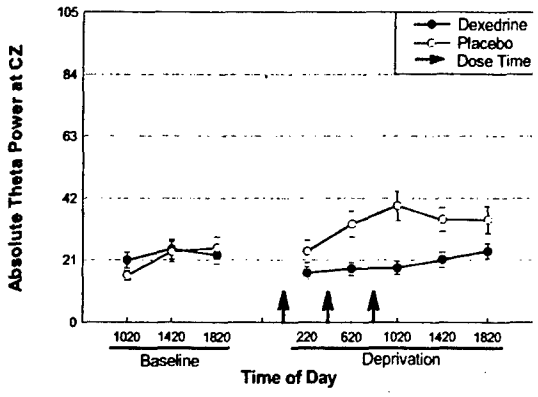

Figure 2. Fatigue-related increases in theta activity were significantly attenuated by Dexedrine.

POMS mood-disturbance data

Composite mood-disturbance scores under placebo and Dexedrine at four baseline times (1120, 1520, 1920, and 2340) and six deprivation times (0320, 0720, 1120, 1520, 1920, and 2340) from all four studies were analyzed with ANOVAs for study, drug, and time (or session). There was a drug-by-session interaction ($F(5.99,143.68)=16.05$, $p<.0001$) and a drug main effect ($F(1,24)=34.91$, $p<.0001$). Analysis of simple effects revealed no baseline differences, but that mood disturbance scores were significantly lower under the Dexedrine than the placebo condition at every deprivation time from 0335 to 2225 ($p<.05$). The drug main effect was consistent with what was found in the interaction. Overall mood disturbance scores were smaller under Dexedrine than placebo (the means were -7.8 and +5.4, respectively). Figure 3 graphically depicts the impact of drug and sleep loss on mood ratings.

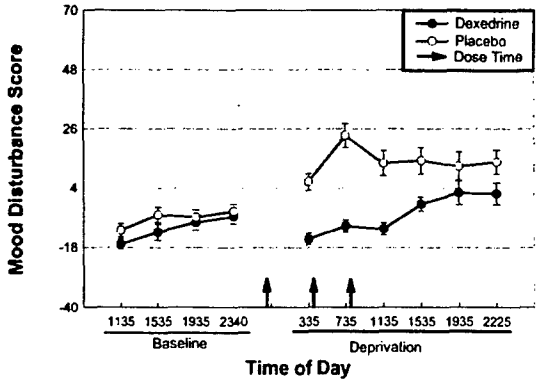

Figure 3. Negative mood scores, indicative of fatigue and confusion, were decreased by Dexedrine.

Polysomnographic data

The sleep-architecture data (percentage of time spent in each sleep stage) were analyzed in a two-way ANOVA for study (the four separate investigations) and night (baseline, Dexedrine recovery, and placebo recovery). This analysis revealed differences across the 3 days on stage 1 sleep ($F(2,48)=65.38$, $p<.0001$), stage 2 sleep ($F(2,48)=12.15$, $p=.0001$), stage 3 sleep ($F(2,48)=9.96$, $p=.0002$), stage 4 sleep ($F(2,48)=16.11$, $p<.0001$), and stage REM sleep ($F(2,48)=23.64$, $p<.0001$). Generally speaking, sleep was better after the deprivation cycles than during baseline. Also, sleep tended to be better after the placebo cycle than the Dexedrine cycle (i.e., less of stages 1 and 2 sleep and more of stage REM sleep after placebo).

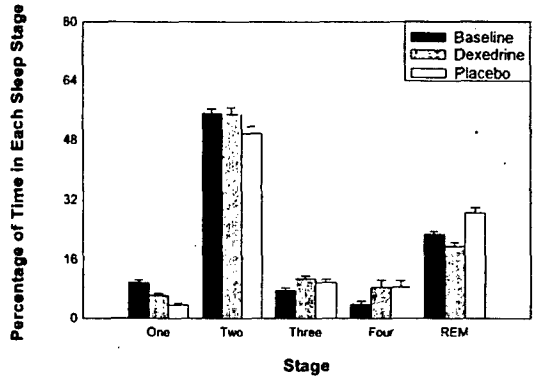

Figure 4. Sleep was slightly more shallow after the Dexedrine cycle than the placebo cycle. Also, there were numerous differences between the baseline night and the postdeprivation nights.

DISCUSSION

This investigation integrated the findings from four previous studies on the efficacy of Dexedrine for maintaining the performance and alertness of sleep-deprived pilots. The results supported earlier conclusions that prophylactic administration of repeated 10-mg doses effectively attenuates the impact of sleep loss on flight performance, mood, and physiological arousal when aviators are kept awake continuously for 40 hours. Effects were particularly noteworthy after 20 to 29 hours without sleep (between 0300 and 1200).

It is noteworthy that very similar patterns of results occurred with each of the four studies, a finding which suggests that data obtained from one group of pilots can be generalized to others despite small sample sizes. There was only one instance of a difference in the magnitude of the drug-related effects as a function of whether the subjects were participating in one study or the other. Although Dexedrine clearly sustained performance despite substantial sleep deprivation throughout all of the assessments, actual in-flight testing was less sensitive to the positive impact of the drug (and the negative impact of sleep loss) compared to simulator testing. As has been discussed elsewhere (Caldwell & Roberts, 2000), this probably resulted from increased

physiological activation in the aircraft versus the simulator (since the consequences of a mistake are more serious in the in-flight environment). Such an arousal increase tends to preserve performance under the placebo condition, making differences between placebo and Dexedrine smaller. Despite this difference in simulator versus in-flight performance, the general pattern of drug effects still indicated that Dexedrine attenuated the performance decline which occurred under placebo. Similar effects were observed in the physiological (EEG) and mood (POMS) data which showed that Dexedrine significantly reduced the adverse impact of sleep loss (regardless of whether the data were collected as part of the in-flight study or as part of the simulator research).

Examination of the overall flight data showed that performance declined substantially under placebo at four out of five deprivation sessions, while performance under Dexedrine did not. This finding, with short-interval 10-mg doses, extends those of Pigeau et al., (1995) who reported that widely spaced 20-mg doses were effective for attenuating initial performance declines and for recovering already-degraded performance.

The EEG data revealed that central-nervous-system (CNS) activation was affected similarly in that Dexedrine preserved EEG activity at more normal levels compared to placebo. Generally speaking, sleepiness and fatigue are known to accentuate the amount of slow-wave brain activity (Pigeau, et al., 1995), and increased theta activity has been associated with generalized performance decrements on cognitive tasks (Belyavin & Wright, 1987) with reduced speed of responding to incoming stimuli (Ogilvie & Simons, 1992). Thus, the fact that Dexedrine not only attenuated theta activity, but maintained theta at predeprivation levels, is a finding that coincides well with the flight-performance results.

POMS mood-disturbance scores revealed a reduction in negative reactions to sleep loss (such as increased anger, depression, fatigue, and confusion) under the Dexedrine treatment. Although there were some sleepiness-related deteriorations in mood under both drug and placebo, it was markedly smaller under Dexedrine. Such findings are consistent with those of Newhouse et al. (1989).

The sleep data from the first night of the study (baseline) and the recovery nights following the two deprivation cycles indicated that there was some cost associated with Dexedrine administration. Dexedrine decreased the restfulness of the recovery periods by increasing the amount of time that subjects spent in the lighter stages of sleep. Also, Dexedrine substantially reduced the amount of REM sleep relative to what was seen during baseline and the post-placebo recovery period. Whether the lighter sleep under Dexedrine would be of concern in actual field operations is difficult to know, but the size of the effects suggests that problems would be minimal as long as the sleep period was not restricted to less than 8 hours. The impact of altered REM sleep during recovery is unclear since the function of REM sleep is not fully understood (Lubin, Moses, Johnson, & Naitoh, 1974; Johnson, Naitoh, Moses, & Lubin, 1974). If REM sleep consolidates memory and/or restores mental resources, repeated use of Dexedrine might lead to a progressive deterioration of higher-level thought processes. However, it seems unlikely that this would rapidly manifest itself as long as 1 night of recovery sleep (8 hours in length) is allowed after 40 hours of continuous wakefulness (Caldwell & Caldwell, 1997b).

SUMMARY AND CONCLUSIONS

Dexedrine has for years been proven effective for maintaining the performance of fatigued people in non-aviation settings (Weiss & Laties, 1967). The present findings show that Dexedrine is likewise effective in sleep-deprived aviators, and that the effects seen in one sample of pilots generalize easily to others. Such results suggest that well-controlled administration of dextroamphetamine is an appropriate fatigue countermeasure for intense and unpredictable sustained operations. The results of the present analysis support an earlier contention by Cornum, Caldwell, & Cornum (1997) that well-controlled administration of amphetamine, restricted to short- to moderate-term circumstances in which heavily fatigued aviators must perform continuously, "may make the difference between a mission completed safely and effectively, and one that ends in disaster" (p 57). However, it must be re-emphasized that no stimulant can replace effective crew-rest scheduling or provide a substitute for restful, restorative sleep.

DISCLAIMER

The opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army and/or the Department of Defense.

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